Optimizing Fluid Resuscitation and Preventing Fluid Overload in Patients with Septic Shock

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Abstract

Intravenous fluid administration remains an important component in the care of patients with septic shock. A common error in the treatment of septic shock is the use of excessive fluid in an effort to overcome *both* hypovolemia and vasoplegia. While fluids are necessary to help correct the intravascular depletion, vasopressors should be concomitantly administered to address vasoplegia. Excessive fluid administration is associated with worse outcomes in septic shock, so great care should be taken when deciding how much fluid to give these vulnerable patients. Simple or strict "recipes" which mandate an exact amount of fluid to administer, even when weight based, are not associated with better outcomes and therefore should be avoided. Determining the correct amount of fluid requires the clinician to repeatedly assess and consider multiple variables, including the fluid deficit, organ dysfunction, tolerance of additional fluid, and overall trajectory of the shock state. Dynamic indices, often involving the interaction between the cardiovascular and respiratory systems, appear to be superior to traditional static indices such as central venous pressure for assessing fluid responsiveness. Point-of-care ultrasound offers the bedside clinician a multitude of applications which are useful in determining fluid administration in septic shock. In summary, prevention of fluid overload in septic shock patients is extremely important, and requires the careful attention of the entire critical care team.

Keywords

- septic shock
- fluid resuscitation
- fluid overload
- point-of-care ultrasound
- sepsis guidelines

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Pathogenesis of Hypovolemia in Sepsis

Sepsis causes hypovolemia due to vasodilation and endothelial dysfunction leading to increased vascular permeability and leakage of water into the extravascular space.[1,2] An increase in endothelial permeability results in progressive third spacing of fluid, which leads to more fluid administration, which in turn leads to increased transmural vascular leakage into tissues resulting in a vicious cycle of worsening organ edema, system dysfunction, and increased risk of mortality.

Sepsis and septic shock were previously considered strictly volume depleted states. To this day, fluid resuscitation remains a part of the primary treatment of septic patients along with the administration of antibiotics and vasoactive agents. However, we have developed a more nuanced understanding of the complex mechanisms leading to hypotension in sepsis.

Vasoplegia, rather than hypovolemia, has been identified as the leading mechanism in the development of septic shock. Profound venodilation in vascular beds decreases venous return and thus cardiac output. Sepsis induces activation of endothelial adhesion molecules resulting in the activation of the coagulation cascade, platelets, and leukocytes leading to microvascular thrombi and endothelial injury.[3] More recent evidence has emerged suggesting that the mechanism of vascular permeability in sepsis is related to the degradation of the endothelial glycocalyx.[4] Aggressive fluid administration leading to hypervolemia may cause iatrogenic worsening of glycocalyx degradation and is associated with increased in-hospital mortality.[5]

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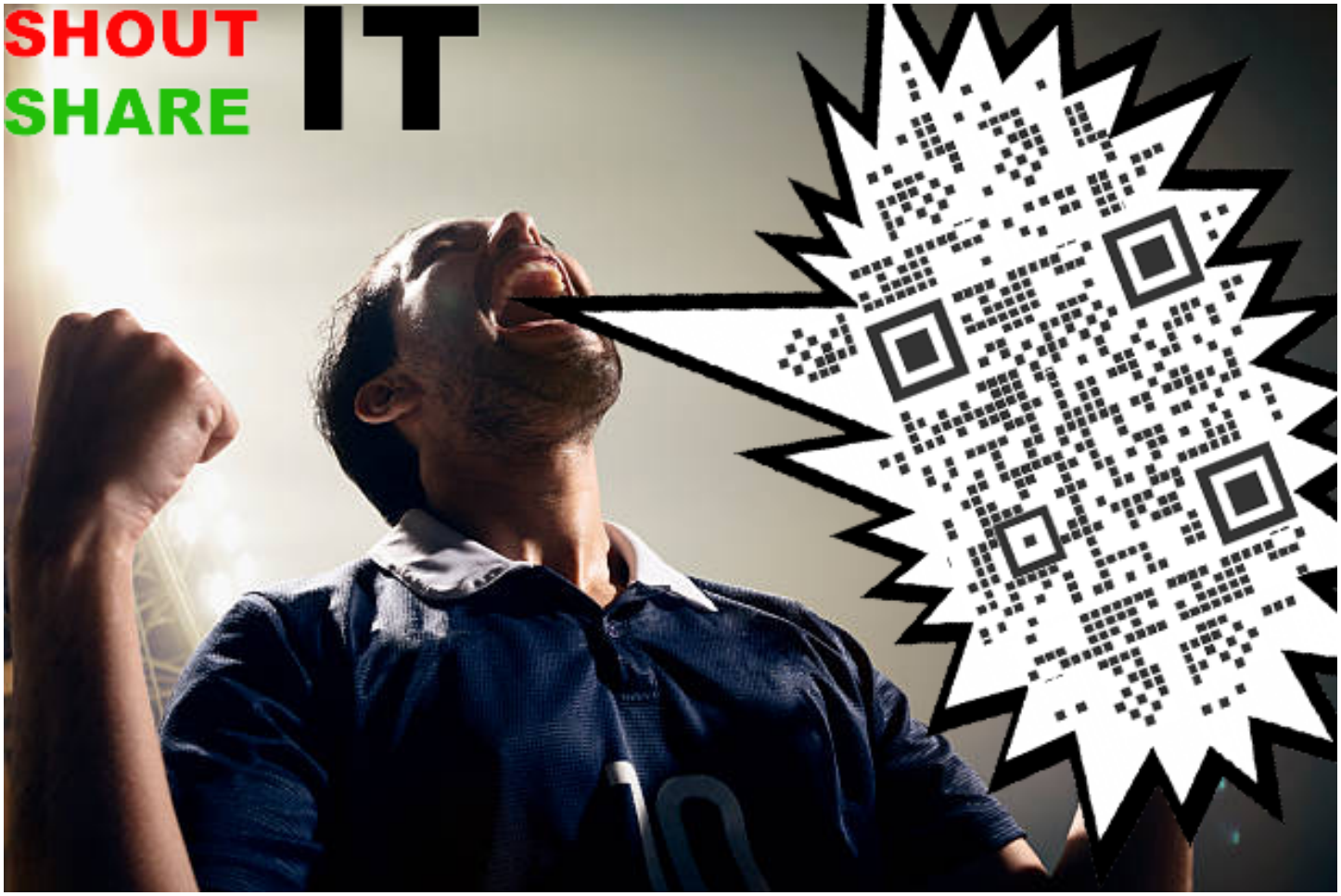
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The goal of volume resuscitation is to increase stroke volume (SV). If an increase in SV is not achieved, volume loading serves no benefit and may be detrimental. According to the Frank-Starling principle, an increase in preload increases SV in a linear manner until optimal preload is achieved. Once there is no longer any preload reserve and the ventricular function curve flattens out, further fluid infusion has little effect on the SV. Hemodynamic response to IV fluid is determined by several factors such as mean systemic filling pressure, cardiac chamber filling pressures, ventricular compliance, afterload, and contractility.[6]

Historic Perspective

A randomized trial examining the benefit of early goal-directed therapy (EGDT) was conducted in 2001 by Rivers et al.[7] In this trial, a bundled approach to sepsis consisting of fluid resuscitation and antimicrobial strategies administered in a timely manner guided by physiologic end points was compared with standard of care and a 16% absolute risk reduction in mortality was noted. Patients assigned to the EGDT arm were treated in the emergency department by the researchers for the first 6 hours prior to admission to the intensive care unit (ICU). Treatment strategies included 500-mL boluses of crystalloid every 30 minutes to achieve a central venous pressure (CVP) of 8 to 12 mm Hg, vasopressors to maintain a mean arterial pressure (MAP) of at least 65 mm Hg, transfusion of red blood cells to achieve a hematocrit of at least 30% followed by Dobutamine administration if the central venous oxygen saturation ($ScvO_2$) was less than 70%, and mechanical ventilation with sedative administration to decrease oxygen consumption. Observational studies were performed that demonstrated survival benefits using EGDT[8,9]; however, the original single-center study remained the only randomized, controlled trial for over a decade. The EGDT methodologies were adopted by the Surviving Sepsis Campaign (SSC) and, more recently, the Centers for Medicare and Medicaid Services' SEP-1 mandates —both of which recommend 30 mL/kg IV crystalloid fluid in the first 3 hours despite the fact that fluid administration was not the only intervention being evaluated in the Rivers trial.[10,11]

Evidence supporting early liberal intravenous fluid resuscitation is equivocal and its value within sepsis treatment bundles is difficult to ascertain.[12] The strength of statistical as well as clinical evidence to support EGDT is low.[13] The mortality benefit in the EGDT trials can be attributed solely to early administration of antibiotics rather than IV fluids or other components of the bundles.[14] While early antibiotic administration was strongly supported by numerous studies,[15–18] the widespread implementation of sepsis treatment bundles led to overly liberal intravenous fluid administration and increased use of vasoactive medications and blood transfusions. Additionally, the treatment components were not suitable to all and patients with higher severity of sepsis fared worse with EGDT.[14] This was attributed to their increased susceptibility to complications associated with the components of a fixed, standard hemodynamic resuscitation. Examples of such complications include fluid overload due to volume in the setting of underlying cardiac dysfunction, arrhythmias due to inotropes/vasopressors, transfusion-related acute lung injury, and transfusion-related circulatory overload.[19]

High-quality trials examining the benefit of EGDT were lacking until three independent, government-funded, multicenter, randomized controlled trials were conducted between 2014 and 2015—namely, Protocolized Care for Early Septic Shock (ProCESS) from the United States,[20] Australasian Resuscitation in Sepsis Evaluation (ARISE),[21] and Protocolized Management in Sepsis (ProMISe) in the United Kingdom.[22] All three trials concluded that there was no survival benefit of EGDT compared with usual resuscitation. "Usual" resuscitation in sepsis had also evolved considerably and a marked decline in the amount of fluids given in the first 72 hours as well as mortality was noted in these subsequent trials.[3] A 2017 study by Kalil et al evaluated 12 randomized trials and 31 observational studies using a combination of Bayesian and random effects models and concluded that EGDT is not beneficial, and is potentially harmful.[14]

The mortality of septic shock has remained high over the years. An individualized approach to fluid management in sepsis may improve outcomes in sepsis and septic shock.

Timing of Fluid Administration

The ideal timing of initiation of fluids in sepsis or septic shock is unclear. This is due, in part, to the difficulty in disentangling the performance of intravenous fluids within sepsis bundles from the other components, especially antibiotics. Administration of adequate intravenous fluids early in the course of sepsis is recommended as microcirculatory hypoperfusion and organ damage progress with delay in correction of hypovolemia.[23] However, when the effect of fluid administration was analyzed independent of the sepsis bundle, rapid completion of an IV fluid bolus was not found to be associated with a mortality reduction, unlike antibiotic administration.[24] Therefore, fluids should be given as early as possible, but timely initiation of antibiotic therapy should take precedence.

Optimal Volume

While fluid resuscitation is an essential component of sepsis care, deciding the optimal amount of fluid needed by the patient is a challenge. Paradoxically, fluid administration along with the increase in permeability of vessels can result in total body volume overload in septic patients. The landmark FEAST (Fluid Expansion as Supportive Therapy) trial, which randomized children with severe sepsis to receive 40 mL/kg normal saline (NS), 4% albumin, or no fluids provided insight into the detrimental nature of excessive intravenous fluids. A 3.3% increased absolute risk of death in 48 hours in the fluid arms led to early trial closure.[25] Contrary to the expectation, the etiology of death in the fluid arms was noted to be cardiovascular collapse rather than fluid overload.

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Tissue hypoxia and inflammation in sepsis leads to myocardial dysfunction. Diastolic dysfunction (DD) is present in nearly half of patients with septic shock.[26,27] A sixfold increase in mortality has been demonstrated in septic patients with DD when compared with those with normal left ventricular (LF) function.[26] Volume administration in these patients is complex, as there is a narrow window for optimizing fluid status. Patients with LV DD benefit from maintenance of adequate preload and LV filling, but fluid administration can easily precipitate pulmonary edema and hemodynamic compromise.

Much debate surrounds the optimal volume of fluid to administer in sepsis. A growing body of evidence has noted poorer outcomes with the overly liberal intravenous fluid administration of the EGDT era.[28–31] The Vasopressin in Septic Shock Trial (VASST) noted that nonsurvivors received more fluids than survivors when corrected for age, severity of illness, and vasopressor requirement.[31] EGDT patients received an average of over 160 mL/kg of IV fluids in the first 72 hours, while the subsequent EGDT validation trials (ProCESS, ARISE, and ProMISe) administered a relatively modest 98 to 130 mL/kg of IV fluids. The Rivers EGDT trial described a fluid challenge as 20 to 30 mL/kg over 30 minutes while the validation trials used non–weight-based fluid boluses. The SSC and SEP-1 guidelines recommend an initial 30 mL/kg body weight; however, it is not clear whether actual body weight, predicted body weight, or ideal body weight should be used. Even if the guidelines were followed and an empiric 30 mL/kg was to be implemented, the patient's weight may often be an estimate rather than measured in the setting of septic shock and therefore less reliable.[32] The SSC approach to fluid resuscitation and a large positive fluid balance on ICU day 2 have been shown to be independent predictors of death, further emphasizing the need to employ a cautious and tailored approach to decide optimal fluid volume.[30,33]

Each patient's propensity to develop volume overload can vary based on several factors and therefore the amount of fluid administered needs to be individualized. One size does not fit all.[34] Patient-specific factors such as the presence of underlying kidney disease, heart failure (HF), pulmonary disease, or chronic liver disease must be taken into account. Noncompliance with rapid fluid infusion requirements due to clinicians' concern for fluid overload in patients with congestive heart failure, chronic kidney disease, and chronic liver disease has been shown to not worsen mortality.[34] This suggests that patients with underlying illnesses would benefit from customization of fluid administration. Similar concepts apply to patients with sepsis-induced organ dysfunction.

Fluid management in sepsis or septic shock can be complicated in patients with underlying HF. Fluid overload in this patient population can lead to pulmonary edema requiring mechanical ventilation. The susceptibility of the lung to ventilator injury is also increased in sepsis. The cornerstone interventions of HF such as diuretics and noninvasive ventilation may be contraindicated in septic shock. Due to concerns that the 30 mL/kg fluid bolus would send these patients into worsening congestion, noncompliance with standard protocols is more likely, and is appropriate. Among septic patients with concomitant HF with reduced ejection fraction, nonsurvivors have been noted to have received less fluid in the first 6 hours.[35] Therefore, the recommended approach is that these should be assessed for signs of volume overload prior to administration of balanced crystalloids per guidelines, albeit at a reduced infusion rate and lower total volume. Earlier addition of vasopressors or inotropes is appropriate if signs of overload are noted on monitoring of physiologic indices.

Intravenous fluids should be prescribed with rationale and stewardship, in a manner similar to antibiotics. Practical fluid management strategies include early adequate goal-directed fluid management, late conservative fluid management, de-escalation, and late goal-directed fluid removal.[23] Withdrawing or withholding resuscitative fluids should be considered once they are no longer needed.[36] A trend toward shorter duration of intravenous fluid is described by the CLASSIC (Conservative vs. Liberal Fluid Therapy in Septic Shock) trial in which a restrictive fluid strategy was followed after the 30 mL/kg initial resuscitation and fluid boluses were permitted only if severe hypoperfusion occurred. A significant difference was found in the resuscitation volumes when compared with the standard care group at day 5 and during the ICU stay. A trend toward reduced ischemic events, worsening of acute kidney injury, and 90-day mortality was noted, though the trial was not powered to detect differences in these events.[37] Late goal-directed fluid removal, also known as de-resuscitation, involves aggressive and active fluid removal by means of diuretics and renal replacement therapy with net ultrafiltration. Two consecutive days of negative fluid balance within the first week of ICU stay has been found to be an independent predictor of survival in ICU patients.[36] Patients who would potentially benefit from a de-resuscitation strategy can be identified by the absence of preload responsiveness.

Attention should also be paid to the administration of nonresuscitation fluids. Several studies indicate that a majority of the fluids received by a patient in septic shock are given for indications other than volume expansion such as drugs, parenteral nutrition, and vehicles for intravenous medications.[37] Nonresuscitation fluids constitute a major fraction of fluids administered, particularly after day 2. Models have suggested that a reduction in fluids of around 3 L can be obtained mainly through reducing these non-resuscitative fluids.[38]

Fluid Choice

Current guidelines recommend crystalloids as the initial fluid solution of choice in the resuscitation of patients with sepsis or septic shock. Guidelines also suggest the use of balanced fluid solutions and the addition of albumin when patients are requiring larger amounts of crystalloids.[11] Some of these guidelines are based on low-quality evidence and therefore the question of which fluid should be used for septic shock is still a matter of considerable debate.

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Approaching fluid choice as crystalloid versus colloid might be overly simplistic. Recent studies have focused on comparing the performance of various crystalloids.

Common crystalloid formulations include balanced fluids such as lactated Ringer's (LR) and plasmalyte and unbalanced fluids such as 0.9% NS and 0.45% saline. These fluids differ in their composition, particularly in the chloride content and strong ion difference. NS has approximately 40% higher chloride content than plasma. Balanced solutions better resemble plasma composition. NS is the crystalloid most routinely used for resuscitation in sepsis and as the "control" fluid in large randomized trials. The use of NS in resuscitation induces hyperchloremic metabolic acidosis, which has deleterious effects.[39] Patients in septic shock often suffer from lactic acidosis; so, the addition of a hyperchloremic acidosis has the potential to drive the pH down to dangerous levels. Resuscitation with chloride-liberal intravenous fluids is associated with an increased incidence of acute kidney injury when compared with a chloride-restrictive strategy.[40] Improvement in patient-centered outcomes and mortality benefit has been demonstrated with the use of balanced fluids in resuscitation.[41–43]

Colloid solutions contain larger molecules of higher weight that tend to remain in the intravascular compartment due to their inability to cross the capillary membrane. Examples of colloids include human albumin and semi synthetic products such as hydroxyethyl starch, dextran, and gelatin. While colloids are considered more potent volume expanders, evidence to support survival benefit from their use is lacking. They are associated with increased length of stay and cost.[41] Strong evidence is present to suggest that semisynthetic colloids may cause renal failure, coagulopathy, anaphylactoid reactions, and decreased survival.[42,44] Their use should therefore be avoided. The role of albumin is less clear. The SAFE trial compared 4% albumin versus NS in severe sepsis among all ICU patients. In a subgroup analysis of patients with severe sepsis, the SAFE investigators noted a reduction in 28-day mortality in the albumin group, but this reduction did not achieve statistical significance.[45]

Fluid versus Vasopressors

Another source of controversy in sepsis care has been the use of vasopressors early in the clinical course. The CENSER (Early Use of Norepinephrine in Septic Shock Resuscitation) trial noted increased shock control by 6 hours with early norepinephrine use.[46] On the contrary, the recent VOLUME-CHASERS study found that increasing doses of vasopressors in the first 6 hours of severe sepsis or septic shock is associated with increased mortality unless paired with at least 2 L of crystalloid resuscitation.[47] A balanced approach of "filling the tank" with fluid, while "squeezing the pipes" with vasopressors, seems logical. Further studies are necessary to better define the appropriate balance between vasopressors and fluid administration.

The CLOVERS (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) trial aims to determine the impact of a restrictive fluid strategy where vasopressors will be utilized first followed by fluids in sepsis-induced hypotension as compared with a liberal fluid strategy where fluids will be used first followed by rescue vasopressors.[48]

Guiding Optimal Resuscitation

Fluid administration in sepsis has a narrow therapeutic margin. The risks of worsening hypoperfusion and over-resuscitation must be balanced. Moreover, only approximately 50% of unstable critically ill patients will be responsive to fluid administration.[49] Adequate assessment of perfusion and fluid responsiveness are of paramount importance in the resuscitation of these patients. Fluid responsiveness is generally accepted to mean the potential for a significant increase in cardiac output following the administration of a fluid bolus. Most studies of fluid responsiveness use an increase of at least 15 or 20% to constitute a "significant" increase in SV or cardiac output.

While the clinical presentation of septic shock might be obvious, subclinical hypoperfusion in sepsis may be more subtle. Clinical indices such as heart rate, blood pressure, arterial oxygen saturation, respiratory rate, mentation, capillary refill, skin mottling, temperature of extremities, and urine output often provide clues suggestive of tissue hypoperfusion. A target MAP of over 65 mm Hg is recommended in patients with septic shock requiring vasopressor use.[11] In patients with sepsis, however, a fluid challenge may increase SV but lead to further vasodilation or decrease in systemic vascular resistance. In these cases, the MAP alone may not be reflective of the overall hemodynamic situation.

Several randomized clinical trials have evaluated the role of serum lactate in the resuscitation of patients with septic shock and a significant mortality benefit is observed with lactate-guided resuscitation.[50–54] While increased lactate levels are associated with worse outcomes, elevation of serum lactate in sepsis is not always due to impaired tissue perfusion. Serum lactate is a surrogate marker for tissue perfusion and not a direct measure. Sepsis-associated hyperlactatemia may also arise from excessive β-adrenergic stimulation leading to accelerated aerobic glycolysis that worsens with disease severity.[55] Regardless, normalization of lactate has been incorporated as a treatment endpoint by the surviving sepsis campaign and an elevated lactate ($>$2 mmol/L) requires resuscitation and re-measurement within 2 to 4 hours.[56]

The Rivers protocol relied on the measurement of CVP and $ScvO_2$ which involved placement of a central venous catheter. The idea was that CVP was a surrogate measure of cardiac filling pressures (or preload) and that this would identify patients with fluid-responsive hypovolemia thereby guiding resuscitation. It has since been recognized that the use of CVP or other static measurements of right or left heart pressures or volumes cannot be justified due to the limited ability to predict fluid responsiveness when such variables are within a normal range.[57–59] This is due to the fact that changes in intrathoracic pressure, ventricular compliance, and venous tone continually occur in critical illness. In fact, the CVP, a

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change in CVP in response to fluid bolus, and pulmonary capillary wedge pressure (PCWP) were all found to poorly predict fluid responsiveness.[60] CVP has utility only as a stopping rule for fluid administration (CVP > 8 mm Hg).[61] Pulmonary artery catheters are no longer routinely used in the management of septic shock, as they were associated with increased resource utilization and higher mortality in septic patients.[62]

The most recent iteration of the Surviving Sepsis Guidelines notes these findings and recommends the use of dynamic over static variables of fluid responsiveness.[11] Dynamic markers of fluid responsiveness have demonstrated better diagnostic accuracy at identifying patients who are likely to respond to a fluid challenge by increasing their SV.[63] These methods use the cyclical dynamic changes to cardiovascular physiology seen during mechanical ventilation. During positive pressure ventilation, the increase in intrathoracic pressure has opposing effects on the LV and the right ventricle (RV). During inspiration, the brief compression of pulmonary vascular beds results in an increase in the LV preload and the elevated intrathoracic pressure decreases the transmural gradient thereby decreasing LV afterload. LF SV and pulse pressure (PP) therefore increase in inspiration. The elevated intrathoracic pressure during inspiration causes an increase in RV afterload due to elevated alveolar pressure and a decrease in RV preload due to the opposition of venous return. This decreased column of RV output eventually reaches the left side of the heart and manifests as reduced LV preload which in turn results in a decrease in the LV SV and PP during expiration. When patients are in a hypovolemic and fluid responsive state, these normal respirophasic variations are more pronounced.

A large number of studies support the use of pulse pressure variation (PPV) derived from the arterial waveform, stroke volume variation (SVV) derived from pulse contour analysis, and variations in the pulse oximeter waveform in the assessment of fluid responsiveness.[49,64] PPV and SVV are calculated as the difference between maximal and minimal PP or SV, respectively. Variation of greater than 12 to 13% in PPV or SVV has been found highly accurate in predicting fluid responsiveness with sensitivity, specificity, and diagnostic odds ratios of 0.89, 0.88, and 59.86 for PPV and 0.82, 0.86, and 27.34 for SVV, respectively.[49] The pulse oximetry plethysmographic waveform measures changes in volume unlike the arterial waveforms which measure pressure. Dynamic changes to both the peak and the amplitude of the pulse oximetry waveform have shown good correlation with PPV and accurately predict fluid responsiveness.[64,65]

Limitations do exist in using dynamic indices to predict fluid responsiveness. The patient must be mechanically ventilated and passively receiving breaths from the ventilator, as spontaneous respiratory efforts will alter the calculated values and their interpretation. The magnitude of change varies with tidal volume with most studies using larger tidal volumes of 8 to 10 mL/kg. Smaller studies in acute respiratory distress syndrome patients suggest that PPV can be indicative of fluid responsiveness with low tidal volume/high positive end-expiratory pressure ventilation, but robust data are currently lacking.[66] Finally, the presence of cardiac arrhythmias precludes the use of PPV or SVV, as the presence of ectopy would alter beat-to-beat diastolic filling.

Ultrasound-Guided Fluid Management in Sepsis

Ultrasound offers physicians the ability to perform real-time and repeated bedside assessments of the patient's hemodynamic variables and volume status. The combination of inferior vena cava (IVC) ultrasound, lung ultrasound, and echocardiography can provide an accurate assessment of volume status and fluid responsiveness. In patients presenting in septic shock, an initial assessment using point-of-care echocardiography must be performed prior to tests for fluid responsiveness to rule out obstruction to venous return and interstitial syndrome, assess biventricular function, and form a rational treatment strategy.

Measurement of the IVC diameter (dIVC) by ultrasound is fast and noninvasive. The dIVC varies with the phase of respiration. In normal, spontaneously breathing patients, it decreases by approximately 50% during tidal breathing in inspiration. Conversely, during positive pressure ventilation, the dIVC increases by around 50% in inspiration. The use of dIVC and caval indices (IVC collapsibility or distensibility) in the assessment of volume status and fluid responsiveness has been a matter of much debate without clear evidence to support or prevent their routine use. Static measurement of the maximal dIVC has been found to be unhelpful in predicting fluid status.[67] Small, single-center studies noted that dynamic respirophasic change (distensibility) of greater than 12% identified fluid responsiveness in mechanically ventilated critically ill patients.[68,69] dIVC was also shown to be predictive of fluid responsiveness in spontaneously breathing patients with sepsis and cardiac arrhythmias.[70,71] More recent studies, however, have found that ultrasound evaluation of the dIVC and its respiratory variations are inaccurate methods for predicting fluid responsiveness.[72–74] The actual dIVC measurement itself is easily influenced by the location of probe placement and measurement, coexisting conditions causing elevated intra-abdominal or intrathoracic pressures, nonuniform collapse of the IVC, and the operator experience. These factors give rise to wide variability and inaccurate results. The utility of dIVC may reside in the extreme scenarios.[75] In a patient with septic shock, a narrow, collapsing IVC (diameter < 1.2 cm) warrants fluid administration and a wide IVC (> 2.5 cm) with no variability favors withholding additional fluids. As with any other index, serial measurements and taking into account the clinical context improves its usefulness.

The passive leg raise (PLR) test is an excellent dynamic index of fluid responsiveness.[76,77] PLR is appealing in its simplicity: it resembles a "self" fluid bolus, and it can be used in patients with contraindications to fluids, as it is reversible upon returning the legs to their original position. The maneuver consists of an initial assessment of the cardiac output (or SV) using echocardiography with the patient's head of bed at 45 degrees, followed by putting the head of bed

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at 0 degrees and lifting the patient's legs passively up to a 45-degree elevation followed by cardiac output (or SV) re-measurement. This maneuver provides an "auto-transfusion" of several hundred mL of blood to the central compartment, mimicking what the cardiovascular system would experience if actual fluid would be given. The left ventricular outflow tract (LVOT) velocity time integral (VTI) is the most common method for echocardiographic measurement of SV, and VTI before and after PLR has been shown in multiple studies to be an accurate predictor of fluid responsiveness.[78–80] A 12% or greater increase in the value has a sensitivity of 0.69 to 0.77 and a specificity of 0.89 to 1.00 for a favorable response to fluid bolus. PLR can be very useful in the initial stages of resuscitation in the emergency room or in spontaneously breathing patients. The effect of PLR persists over several breaths. The actual response to preload increase is assessed rather than predictions based on cardiopulmonary interactions and therefore it can also be used in mechanically ventilated patients or patients with an arrhythmia in whom PPV is not useful.[80] A major limitation in using PLR alone is that severely hypovolemic patients may not mobilize a sufficient enough amount of their blood volume to manifest a change in cardiac output. Another limitation is it cannot be used in the presence of elevated intra-abdominal pressure as venous return is impaired and fluid responsiveness cannot be accurately determined.[81] Finally, inconsistencies in Doppler gate location and orientation may limit the interoperator reliability of the LVOT VTI. Changes in carotid artery Doppler flow following a PLR or fluid challenge is highly predictive of fluid responsiveness with studies demonstrating superior performance to SVV, PPV, and PLR.[82,83] This is measured as the respirophasic variation in the carotid Doppler peak velocity and a greater than 20% value has been found highly predictive of volume responsiveness (sensitivity: 0.94, specificity: 0.86).

Bedside lung ultrasound is a useful tool in the assessment of the patient's fluid tolerance. The presence of extravascular lung water (EVLW) due to a positive net fluid balance is associated with higher mortality in sepsis.[31] Lung sonography can be used to monitor for the development of sonographic B lines when fluids are being administered.[84] The number of B lines has been shown to correlate directly with the amount of EVLW and inversely with oxygenation and PaO_2/FiO_2 ratio.[85] Baseline lung ultrasound evaluation might also identify patients with sepsis who are at increased risk for developing hypoxemia within 72 hours of hospitalization.[86]

Conclusion and Recommendations

Intravenous fluid administration remains an important component in the care of patients with septic shock. A common error in treatment of septic shock is the use of excessive fluid in an effort to overcome *both* hypovolemia and vasoplegia. While fluids are necessary to help correct the intravascular depletion, vasopressors should be concomitantly administered to address vasoplegia. Excessive fluid administration is associated with worse outcomes in septic shock, so great care should be taken when deciding how much fluid to give to these vulnerable patients. Simple or strict "recipes" which mandate an exact amount of fluid to administer, even when weight based, are not associated with better outcomes and therefore should be avoided. Determining the correct amount of fluid requires the clinician to repeatedly assess and consider multiple variables, including the fluid deficit, organ dysfunction, tolerance of additional fluid, and overall trajectory of the shock state. Dynamic indices, often involving the interaction between the cardiovascular and respiratory systems, appear to be superior to traditional static indices such as CVP for assessing fluid responsiveness. Point-of-care ultrasound offers the bedside clinician a multitude of applications which are useful in determining fluid administration in septic shock. In summary, prevention of fluid overload in septic shock patients is extremely important, and requires the careful attention of the entire critical care team.

Conflict of Interest
None declared.

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